

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 January 2001 (11.01.2001)

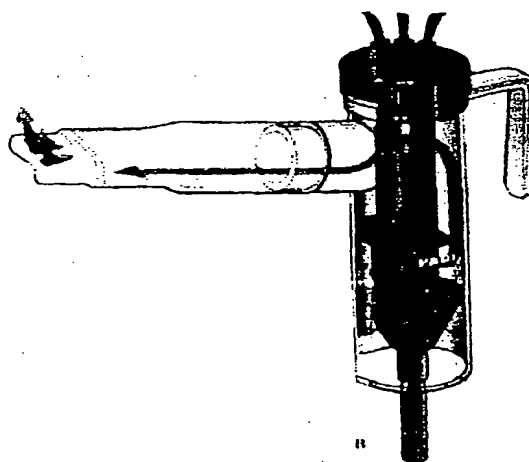
PCT

(10) International Publication Number
WO 01/02024 A1

- (51) International Patent Classification⁷: A61L 9/04 (71) Applicant (for all designated States except US): SINUS-PHARMACY.COM [US/US]; 6420 Via Real, Suite 7, Carpinteria, CA 93013 (US).
- (21) International Application Number: PCT/US00/18410
- (22) International Filing Date: 5 July 2000 (05.07.2000) (72) Inventors; and
- (25) Filing Language: English (75) Inventors/Applicants (for US only): OSBAKKEN, Robert, S. [US/US]; 5388 Cherry Ridge Drive, Camarillo, CA 93012 (US). HALE, Mary, Anne [US/US]; 23088 Leonara Drive, Woodlands Hills, CA 91367 (US). LEIVO, Frederick, T. [US/US]; 654 Oak Avenue, Carpinteria, CA 93013 (US). MUNK, James, D. [US/US]; 4907 Via Cupertino, Camarillo, CA 93012 (US).
- (26) Publication Language: English
- (30) Priority Data:
- | | | |
|------------|---------------------------|----|
| 60/142,618 | 6 July 1999 (06.07.1999) | US |
| 60/142,620 | 6 July 1999 (06.07.1999) | US |
| 60/142,621 | 6 July 1999 (06.07.1999) | US |
| 60/142,622 | 6 July 1999 (06.07.1999) | US |
| 60/142,624 | 6 July 1999 (06.07.1999) | US |
| 60/142,741 | 6 July 1999 (06.07.1999) | US |
| 60/142,881 | 6 July 1999 (06.07.1999) | US |
| 60/193,507 | 3 April 2000 (03.04.2000) | US |
| 60/193,508 | 3 April 2000 (03.04.2000) | US |
| 60/193,509 | 3 April 2000 (03.04.2000) | US |
| 60/193,510 | 3 April 2000 (03.04.2000) | US |
| 60/194,078 | 3 April 2000 (03.04.2000) | US |
| 09/577,623 | 25 May 2000 (25.05.2000) | US |
- (74) Agent: TUSCAN, Michael, S.; Morgan, Lewis & Bockius LLP, 1800 M Street, N.W., Washington, DC 20036-5869 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: AEROSOLIZED ANTI-INFECTIVES, ANTI-INFLAMMATORIES, AND DECONGESTANTS FOR THE TREATMENT OF SINUSITIS



(57) Abstract: Pharmaceutical compositions are described that comprise one or more active ingredients selected from the group consisting of anti-infective, anti-inflammatory and anti-mucolytic agents, and particularly to compositions formulated as a solution in a unit dose for aerosol administration to treat chronic sinusitis. The figure discloses the preferred equipment for aerosolized delivery of pharmaceutical solutions. This nebulizer, manufactured by Pari Respiratory Equipment, Inc., for the inventors, produces the desired particle size for affective administration of the solutions in this invention to the sinuses. To use this nebulizer preferably medication is placed in the nebulizer at (A). The nebulizer is then connected to compressor or other source at (B) with tubing supplied. When the airflow is turned on, the patient places the nose piece (C) under their nostrils and breathes normally until the medication solution in the nebulizer begins to sputter and no mist comes out at (C).

Best Available Copy



WO 01/02024 A1



(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

— With amended claims.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— With international search report.

TITLE: **Aerosolized Anti-Infectives, Anti-Inflammatories, and
Decongestants for the Treatment of Sinusitis**

RELATED APPLICATIONS

This application is a Continuation-In-Part of U.S. Application 09/577,623, filed May 25, 2000, and claims the benefit of U.S. Provisional Applications 60/142,618, 60/142,620, 60/142,621, 60/142,622, 60/142,624, 60/142,741, and 60/142,881, all filed on July 6, 1999, and of U.S. Provisional Applications 60/193,507, 60/193,508, 60/193,509, 60/193,510, and 60/194,078, all filed on April 3, 2000, which are hereby incorporated by reference in their entireties.

TECHNICAL FIELD

The present invention relates to pharmaceutical compositions comprising one or more active ingredients selected from the group consisting of anti-infective, anti-inflammatory and anti-mucolytic agents, and particularly to compositions formulated as a solution in a unit dose or multi-dose vials for aerosol administration to treat chronic sinusitis.

BACKGROUND OF THE INVENTION

There are a number of air-filled cavities called sinuses in the skull (*Stedman's Medical Dictionary, 27th Edition*, page 1644, (1999), Lippincott Williams & Wilkins, Baltimore, Maryland). Four pairs of sinuses known as the paranasal sinuses, connect the space (known as the nasal passage) running from the nostrils and up through the nose. These four pairs of paranasal sinuses are the frontal sinuses, the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinuses. They are located, respectively, in the forehead, behind the cheekbones, between the eyes, and behind the eyes. A membrane

lining the sinuses secretes mucus, which drains into the nasal passage from a small channel in each sinus. Healthy sinuses are sterile and contain no bacteria. In contrast, the nasal passage normally contains many bacteria that enter through the nostrils as a person breathes.

A number of factors and/or processes are involved in maintaining healthy sinuses. The mucus secreted by the membrane lining must be fluid but sticky, in order to flow freely yet absorb pollutants and entrap bacteria. It must also contain sufficient amounts of bacteria-fighting substances, such as antibodies. Additionally, small hair-like projections called cilia, located in the nostril, must beat in unison to propel mucus outward, in order to expel bacteria and other particles. Moreover, the mucous membranes themselves must be intact, and the sinus passages must be open to allow drainage and the circulation of air through the nasal passage. When one or more of these processes or factors are amiss, causing obstruction of the sinus passage, an infection called sinusitis develops.

Sinusitis is an inflammation of the membrane lining one or more paranasal sinuses. There are three different types of sinusitis: acute, recurrent acute, and chronic. Acute sinusitis is characterized as lasting less than three weeks or occurring less than four times a year. Acute sinusitis can be successfully treated using antibiotics, leaving no damage to the linings of the sinus tissue. Recurrent acute sinusitis occurs more often but leaves no significant damage. Chronic sinusitis lasts longer than three weeks and often continues for months. In cases of chronic sinusitis, there is usually tissue damage. According to the Center for Disease Control (CDC), thirty seven million cases of chronic sinusitis are reported annually.

Causes of Sinusitis

The most common cause for sinusitis is a viral cold or flu that infects the upper respiratory tract and causes obstruction. Obstruction creates an environment that is hospitable for bacteria, the primary cause of acute sinusitis (Etkins *et al.*, 1999 *Nidus Information Services, Inc. Well-Connected Report: Sinusitis*. June 1999. (Online) www.well-connected.com.). The bacteria most commonly found in acute sinusitis are

Streptococcus pneumoniae (also called pneumococcal pneumonia or pneumococci), *H. influenzae* (a common bacteria associated with many respiratory infections in young children), and *Moraxella* (or *Branhamella*) *catarrhalis*. Less common bacterial culprits include *Pseudomonas* and other streptococcal strains including *Staphylococcus aureus*.

Fungi are an uncommon cause of sinusitis, but its incidence is increasing. The fungus *Aspergillus* is the common cause of fungal sinusitis. Others include *Curvularia*, *Bipolaris*, *Exserohilum*, and *Mucormycosis*. Fungal infections can be very serious and should be suspected in people with sinusitis who also have diabetes, leukemia, AIDS, or other conditions that impair the immune systems. Fungal infections can also occur in patients with healthy immune systems. There have been a few reports of fungal sinusitis caused by *Metarrhizium anisopliae* which is used in biological insect control.

Chronic or recurrent acute sinusitis can be a lifelong condition and may result from untreated acute sinusitis that causes damage to the mucous membranes, medical disorders that cause chronic thickened stagnant mucus, or abnormalities in the nasal passage such as polyps, enlarged adenoids, cleft palate, or tumors. The same organisms that cause acute sinusitis are often present in chronic sinusitis. In addition, about 20% of chronic sinusitis cases (Etkins *et al.*, 1999, *Id.*) are caused by *Staphylococcus aureus* (commonly called Staph infection). Along with these bacteria, certain anaerobic bacteria, particularly the species *Peptostreptococcus*, *Fusobacterium*, and *Prevotella*, are found in 88% of cultures in chronic sinusitis cases (Etkins *et al.*, 1999, *Id.*). Fungi can also cause chronic and recurrent sinusitis. An uncommon form of chronic and highly recurrent sinusitis is caused by an allergic reaction to fungi, usually, *aspergillus*, growing in the sinus cavities. Fungal sinusitis usually occurs in younger people with healthy immune systems and is more likely to be found in warm climates.

Symptoms of Sinusitis

In acute sinusitis, symptoms almost always present are nasal congestion and discharge which is typically thick and contains pus that is yellowish to yellow-green. Severe headache occurs, and there is pain in the face. A persistent cough occurs

particularly during the day. Other upper respiratory symptoms and fever may be present. Sneezing, sore throat, muscle aches, and fatigue are rarely caused by sinusitis itself, but may result from symptoms or causes, such as muscle aches caused by fever, sore throat caused by post-nasal drip, and sneezing resulting from allergies.

The symptoms of recurrent acute and chronic sinusitis tend to be vague and generalized, last longer than eight weeks, and occur throughout the year, even during nonallergy seasons. Nasal congestion and obstruction are common. Yellowish discharge, chronic cough, bad breath, and postnasal drip may occur. Sufferers do not usually experience facial pain unless the infection is in the frontal sinuses, which results in a dull, constant ache. However, facial tenderness or pressure may be present.

Site-specific symptoms depend on the location of the infection. Frontal sinusitis causes pain across the lower forehead. Maxillary sinusitis causes pain over the cheeks and may travel to the teeth, and the hard palate in the mouth sometimes becomes swollen. Ethmoid sinusitis causes pain behind the eyes and sometimes redness and tenderness in the area across the top of the nose. Sphenoid sinusitis rarely occurs by itself. When it does, the pain may be experienced behind the eyes, across the forehead, or in the face. Rare complications of sinusitis can produce additional symptoms which may be severe or even life threatening.

Treatments of Sinusitis

- The primary objectives for treatment of sinusitis are reduction of swelling, eradication of infection, draining of the sinuses, and ensuring that the sinuses remain open. Less than half of patients reporting symptoms of sinusitis need aggressive treatment and can be cured using home remedies and decongestants alone. Steam inhalation and warm compresses applied over the sinus are often sufficient to relieve discomfort. Many over-the-counter decongestants are available, either in tablet form or as sprays, drops, or vapors, which bring the medication into direct contact with nasal tissue.

Antibiotics are prescribed if decongestants fail to relieve symptoms or if other problems exist, including signs of infection (such as yellowish nasal discharge). They

prevent complications, relieve symptoms, and reduce the risk of chronic sinusitis. Most patients with sinusitis caused by bacteria can be successfully treated with antibiotics used along with a nasal or oral decongestant.

Chronic sinusitis is often difficult to treat successfully, however, as some symptoms persist even after prolonged courses of antibiotics. The usefulness of antibiotics in treating chronic sinusitis is debated. Steroid nasal sprays are commonly used to treat inflammation in chronic sinusitis. For patients with severe chronic sinusitis, a doctor may prescribe steroids, such as prednisone. Since oral steroids can have serious side effects, they are prescribed only when other medications have not been effective.

When medical treatment fails, surgery may be the only alternative in treating chronic sinusitis. Studies suggest that most patients who undergo surgery have fewer symptoms and better life. Presently, the most common surgery done is functional endoscopic sinus surgery, in which the diseased and thickened tissues from the sinuses are removed to allow drainage. This type of surgery is less invasive than conventional sinus surgery, and serious complications are rare.

Considerations and Concerns of Treatments

Sprays, drops, and vapors work quickly but often require frequent administration. Nasal decongestants may dry out the affected areas and damage tissues. With prolonged use, nasal decongestants become ineffective. The tendency is to then increase the frequency of use to as often as once an hour. Withdrawal from the drugs after three to five days of over-frequent use can itself cause symptoms of sinusitis and the return of nasal congestion phenomenon known as rebound effect. Short-acting nasal decongestants may cause rebound effect after only eight hours. Rebound effect leads to dependency when the patient takes the decongestant to treat the rebound effect, the drug becomes ineffective, the patient withdraws, and the condition rebounds again, with the nasal passages becoming swollen and burning. Eventually, the condition can become worse than before the medication was taken. Nasal decongestants are generally recommended for no more than one to three days of use because of this risk.

Some oral decongestants may cause constriction of other vessels in the body, temporarily raising blood pressure in people with hypertension. Other side effects of oral decongestants include insomnia, agitation, abnormal heart rhythms (particularly in people with existing cardiac problems), and urinary retention in men with enlarged prostates. Decongestant sprays and drops, too, are absorbed into the body and can sometimes cause these side effects.

The most common side effect for nearly all antibiotics is gastrointestinal distress. Antibiotics also double the risk for vaginal infections in women. Certain drugs, including some over-the-counter medications, interact with antibiotics, and all antibiotics carry the risk for allergic reactions, which can be serious in some cases. Thus, patients should inform their physician of all medications they are taking and of any drug allergies.

Oral antibiotics are usually prescribed for 7 to 10 days. Patients must take all of the tablets prescribed; failure to do so may increase the risk for reinfection and also for development of antibiotic-resistant bacteria. It should be noted, however, that even after antibiotic treatments, between 10% and 25% of patients still complain of symptoms.

Of major concern to physicians and the public is the emergence of bacterial strains that have become resistant to common antibiotics due to frequent exposure. It should be noted that the average person is not yet endangered by this problem. The risk is greatest in hospitals and nursing homes, but it is still not high. Nonetheless, the prevalence of such antibiotic-resistant bacteria has increased dramatically worldwide, and caution should be exercised.

Nebulization Therapy

Nebulization is a conventional treatment for pulmonary infections related to cystic fibrosis, because it is relatively easy and safe to use, and because it delivers antibiotics topically to the site of infection, with little systemic absorption of the antibiotics. Nebulization has also been known to have been used for sinus infections and pulmonary infections, related to bronchiectasis. Thus, there are few systemic side effects.

Small Aerosolized Particles for Treating Sinusitis:

Yokota *et al.*, *Japanese Journal of Antibiotics* 609(15):48 (1995), reports administration of cefmenoxime using a nebulizer to treat sinusitis patients. These authors evaluated cefmenoxime against clinical isolates from sinusitis patients, and found that minimum inhibitory concentrations were lower when a one percent (1 %) solution was used with a nebulizer. The paper speculates that sufficient concentrations exceeding such minimum inhibitory concentrations would be obtained by nebulizer treatment using a cefmenoxime nasal solution.

Guevara *et al.*, *Anales O. R. L. Iber.-Amer. XVIII*, 3:231-238 (1991), describes aerosol therapy for treating patients suffering from chronic sinusitis. The disclosed aerosol therapy involves delivery of a therapeutic composition comprising 500 mg of Cefotaxime, 5 mg methylprednisolone, and 1.5 ml N-acetylcystine using an air-jet nebulizer for 15-20 minutes, every 8 hours, over a total period of 15 days. The air-jet nebulizer produces aerodynamic particle diameters of average mass of four microns. Guevara *et al.* reports a success rate of 96%. However, Guevara *et al.* does not disclose adding a surfactant to assist deposition, penetration, and retention of the antibiotic in the sinuses. It is also noted that the aerosol therapy of Guevara *et al.* requires frequent treatments over a long period of time.

Kondo *et al.*, *Acta Otolaryngol. Suppl.* 525: 64-67 (1996), reports treatment of paranasal sinusitis using fosfomycin (FOM) aerosol. Kondo *et al.* describes delivery of 4 ml of 3% FOM solution using either a jet-type nebulizer or a ultrasonic nebulizer. The jet-type nebulizer produces aerosol particles having about 0.5 to 0.7 μm in diameter, while the ultrasonic-type nebulizer produces particles having about 2-4 μm in diameter. The results of Kondo *et al.* indicate that the ultrasonic-type nebulizer delivers a higher concentration of FOM to the maxillary sinus surface and is therefore more effective in treating paranasal sinusitis than the jet-type nebulizer. Although Kondo *et al.* suggests that the preferred aerosol particle size is about 2-4 μm in diameter for deposition of a higher level of antibiotic in the maxillary sinus, Kondo *et al.* does not disclose an

administration schedule or the addition of a surfactant to the FOM solution to further increase the deposition of FOM in the sinuses.

Small Aerosolized Particles for Pulmonary Treatment:

Smith *et al.*, U.S. Patent 5,508,269, discloses the use of aminoglycoside aerosol formulations to treat patients suffering from endobronchial infection. Smith *et al.* describes delivery of the aminoglycoside formulation using a jet or ultrasonic nebulizer that produces aerosol particle size between 1 and 5 μm . The formulation comprises 200 to 400 mg of aminoglycoside dissolved in about 5 ml of solution containing 0.225% sodium chloride and it has a pH between 5.5 to 6.5. Although Smith teaches delivery of aminoglycoside to the endobronchial space using a nebulizer for the treatment endobronchial infection, Smith does not teach an aerosol formulation for treatment of sinusitis and does not disclose a treatment schedule. It is also noted that the aerosol particle size disclosed in Smith *et al.* is a broad range. It is not predictable what fraction of the aerosol particles between 1 to 5 μm will deposit in the sinuses, and what fraction of the aerosol particles will have a diameter of 1 μm , 2 μm , *etc.*

Rubin *et al.*, U.S. Patent 5,925,334, describes the use of aerosolized surfactant to promote pulmonary airway clearance. The method of Rubin *et al.* comprises administering a formulation containing a surfactant using a PARI LC Jet nebulizer for 15 minutes, 3 times a day for 14 consecutive days, to patients suffering from bronchitis or cystic fibrosis. However, Rubin does not teach the use of aerosolized antibiotic or aerosolized antibiotic and surfactant combination to treat sinusitis.

Schmitt *et al.*, U.S. Patent 4,950,477, teaches a method of preventing and treating pulmonary infection by fungi using aerosolized polyenes. The method comprises administering to a patient suffering from pulmonary infection by *Aspergillus* about 0.01 mg/kg to 6.0 mg/kg of a polyene in an aerosol of particles having an aerodynamic diameter between about 0.5 μm to about 8 μm . Schmitt *et al.* specifically discloses the administration of amphotericin B. Although Schmitt *et al.* teaches aerosolized polyenes

for treatment of pulmonary infection, Schmitt *et al.* does not provide guidance for using aerosolized polyenes for treating sinusitis.

O'Riordan *et al.*, *Journal of Aerosol Medicine*, 20(1): 13-23 (1997), reports the effect of nebulizer configuration on delivery of aerosolized tobramycin to the lung. O'Riordan *et al.* discloses the delivery of tobramycin using either an ultrasonic nebulizer delivering aerosol particles having between 1.45 to 4.3 μm or a jet nebulizer delivering aerosol particles having about 1.25 μm . The results of O'Riordan *et al.* show that nebulizer configuration affects both the amount of aerosolized tobramycin inhaled as well as the particle size. Specifically, nebulizers that produce large particles are prone to considerable deposition on tubing and connections. O'Riordan *et al.* recommends that nebulizer configuration be specified in treatment protocols.

Large Particle Aerosolization

In contrast to the references discussed above, Negley *et al.*, *ENT Journal*, 78(8):550-554 (1999), and Desrosiers *et al.*, (presented at the ENT Academy Meeting, May 1999) teach large particle nebulization therapy for treatment of sinusitis. Negley observes that deposition of medication into the sinuses is best achieved when the aerosolized particles are 16 to 25 μm in size. Desrosiers *et al.* reports that large particle saline aerosol therapy alone is effective in treating refractory sinusitis and that the addition of tobramycin to the saline solution had minimal benefit.

The journal articles and patents discussed above teach various aerosol therapies for the treatment of sinusitis. However, there does not appear to be agreement among the various authors as to the optimal size or size distribution of the aerosolized particles or even whether antibiotics are effective in treating sinusitis. What has been needed is a clinically effective anti-infective treatment protocol for sinusitis, a more optimal therapy schedule, and an appropriate nebulizer configuration for the deposition of aerosolized anti-infective particles into the sinuses for the successful and consistent treatment of chronic sinusitis.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions that include one or more active ingredients such as anti-infective, anti-inflammatory and anti-mucolytic agents. Such compositions preferably are formulated as a solution in a unit dose or multi-dose vial for aerosol administration to the nasal sinuses. It is contemplated that such formulations are packaged in association with labels or inserts or other forms of directions for their use in the treatment of sinusitis.

In a preferred embodiment, the surface tension of the solution is between about 10 to 70 dynes/cm, in order to yield an aerosol having a preferred Mass Median Aerodynamic Diameter within the range of about 1.0 to 4.0 microns. The use of such an aerosolized spray has minimal systemic side effects. Surface tension of a given formulation may be adjusted by adding a surfactant in addition to the active ingredients in order to bring it into the preferred range.

Generally, it is contemplated that formulations according to the present invention will preferably have a pH in the range of about 3.0 to 8.5; an osmotic pressure of the solution between about 150 mOsm/kg to 880 mOsm/kg; and a NaCl equivalency to the solution is preferably between about 0.9% NaCl to 3.0% NaCl.

Preferred anti-infective agents include Penicillins, Cephalosporins, Macrolides, Sulfonamides, Quinolones, Aminoglycosides, BetaLactam antibiotics, Linezolid, Vancomycin, Amphotericin B, and Azole antifungals. Preferred anti-inflammatory agents include Glucocorticoids, Disodium Cromoglycate and Nedcromil Sodium. Preferred anti-mucolytic agents are Acetylcysteine and Dornase Alpha. Preferred decongestant agents are Phenylephrine, Naphazoline, Oxymetazoline, Tetrahydrozoline and Xylometazoline.

In a preferred embodiment of the invention, a kit is described that provides the various equipment and attachments useful in administering the formulations of the present invention by using the disclosed nebulizer devices.

Preferred administration protocols also are described.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 discloses the preferred equipment for aerosolized delivery of pharmaceutical solutions. This nebulizer, manufactured by Pari Respiratory Equipment, Inc., for the inventors, produces the desired particle size for effective administration of the solutions in this invention to the sinuses. To use this nebulizer preferably medication is placed in the nebulizer at A. The nebulizer is then connected to a compressor or other source at B with tubing supplied. When the airflow is turned on the patient places the nose piece C under their nostrils and breathes normally until the medication solution in the nebulizer begins to sputter and no mist comes out at C.

DETAILED DESCRIPTION OF THE INVENTION

I. General Description

The present invention involves the topical delivery of medications to the nasal cavity and sinuses by aerosolizing aqueous solutions of these medications. The present invention is based in part on the surprising finding that aerosolized anti-infective particles are surprisingly effective therapeutically when they have a mass median aerodynamic diameter (MMAD) of about 3.0 to 3.5 μm for deposition in the sinuses in a preferred size range. The present invention provides an apparatus for delivery of such optimally sized anti-infective particles into the sinuses. The present invention is also based in part on the finding that the addition of a surfactant to formulations increases the deposition, retention, and penetration of anti-infectives or other active ingredients into the sinuses. The present invention provides guidance for therapy schedule and dosage as discussed in detail below.

As described in greater detail below, the pharmaceutical formulations will be aerosolized/atomized prior to administration to a patient to form an aerosol cloud with particles of aerosolized/atomized H_2O and medication that have a MMAD (Mass Median Aerodynamic Diameter) of preferably between about 0.5 and 10 microns, more preferably between about 1.0 to 4.0 microns and most preferably between about 2.0 to 3.5 microns.

It is also preferable to have the maximum number of particles over 5.0 microns be less than 20% of the total particles.

A surprising discovery made by the inventors was that the surface tension of the solution prepared for inhalation needed to be adjusted to achieve optimal results. To achieve effective deposition of medication within the sinuses it is preferable to have the surface tension of the solution for aerosolization be adjusted with surfactants to between 10 dynes/cm and 70 dynes/cm, more preferably between about 20 to 60 dynes/cm, and most preferably between about 30 to 50 dynes/cm.

Contemplated pharmaceutical compositions will include one or more active ingredients such as anti-infective, anti-inflammatory, and anti-mucolytic agents. Appropriate medications to be used in the methods according to the present invention are listed in Table 1. These medications may be administered for the treatment of sinusitis, particularly chronic sinusitis, by resolving infection, reducing inflammation or reducing congestion in the nasal cavity and sinuses.

These compositions ideally will be formulated as a solution in a unit dose or multi-dose vial for aerosol administration to the nasal cavity and sinuses and being packaged with directions for its use in the treatment of sinusitis. Appropriate compositions for this purpose will be formulated by using surfactants, NaCl, or other chemical entities to adjust the solution for administration to have the following properties:

- surface tension preferably between about 10 to 70 dynes/cm, more preferably between about 20 to 60 dynes/cm, and most preferably between about 30 to 50 dynes/cm.
- osmotic pressure between about 200 mOsm/kg to 880 mOsm/kg, more preferably between about 300 mOsm/kg to 700 mOsm/kg and most preferably between about 400 mOsm/kg to 550 mOsm/kg.

- NaCl equivalency of the solution preferably between about 0.2% NaCl and 3.0% NaCl, more preferably between about 0.45% NaCl and 1.8% NaCl and most preferably between about 0.9% NaCl and 1.7% NaCl.
- pH preferably between about 3.0 and 8.5, but may vary according to the properties of the medication used.

A. Surface Tension:

The present inventors have found that the surface tension and, to a lesser degree, particle size are critical factors in getting optimal deposition of the formulation in the nasal cavity and sinuses. For example, particles that are too large will deposit in the nasal cavity, but are unlikely to enter the sinuses. Having too low a surface tension increases an aerosolized particle's chance of deposition on the first surface that it comes in contact with, which generally would be tissue or structures in the nasal cavity proximal to the sinuses. In contrast, if the surface tension is too high much of the aerosolized medication is not deposited within the patient's sinuses and ultimately is deposited in the lungs. If the surface tension is too low most of the aerosolized medication is deposited in the nasal cavity and does not reach the sinuses.

For purposes of preparing formulations according to the present invention, surface tension may be measured by using a Ring Tensiometer or the capillary rise measure method which consists of a capillary tube of known diameter placed into the solution and a measurement of capillary rise taken to provide surface tension. Surface tension may also be measured by Spinning Drop method, Pendant Drop method, Bubble Pressure method, Drop Volume method, and Wilhelmy Plate method. Surface tension will then be adjusted using surfactants to fall within a preferred range in dynes/cm.

B. Osmotic Pressure:

Optimal osmotic pressure helps to reduce damage to the epithelia cilia of the sinuses. Although often not present in chronic sinusitis patients, epithelia cilia perform a useful function in the sinuses by moving mucosal fluid out of the sinuses.

For purposes of preparing formulations according to the present invention, osmotic pressure may be measured by using an Osmometer. If necessary, osmotic pressure may then be raised to fall within a preferred range by adding NaCl, dextrose, or other salts to the solution.

C. Sodium Chloride Equivalency:

Optimal NaCl equivalency (tonicity) works to reduce swelling in the sinuses and nasal cavity by drawing water from the nasal and sinus epithelia, reducing swelling. NaCl equivalency below 0.9 % (hypotonic) may cause swelling in the epithelia of the nasal cavity and sinuses. NaCl equivalency above 3.0% would raise the tonicity and osmotic pressure above desirable levels and may cause a burning sensation.

For purposes of preparing formulations according to the present invention, NaCl equivalency will closely follow osmotic pressure and can be measured using the methods described in section B above.

D. pH:

In general, the pH would be adjusted if a given medication is either more stable or more effective at a certain pH. *American Hospital Formulary Service* (AFHS) published yearly or the *Hand Book of Injectable Drugs* by Lawrence A. Trissel, © 1994 American Society of Hospital Pharmacists, Inc., which are herein incorporated by reference, provide information regarding the stability or effectiveness of a medication at certain pH.

For the purposes of preparing formulations according to the present invention the pH of the various solutions may need to be adjusted to achieve stability or increase effectiveness. A pH meter, where a probe is placed into the solution and the device gives the pH, will be used to measure pH or pH paper will be used to estimate pH by placing solution on the tape and then comparing to a predeveloped chart of pH colorations. When

necessary pH will then be adjusted to arrive at the most preferable range of pH needed for nasal aerosolization by adding buffering agents.

E. General Preparation of a Unit Dose and Production of Aerosol with Optimal Particle Diameter:

After determining the medications to be used in the formulation, each ingredient is weighed/measured out individually, added together, dissolved in sterile water and filtered with a 0.22 micron, 0.45 micron, 1 micron, or 5 micron filter. The preparation is then tested to ensure that it is within the parameters established for surface tension, osmolarity, pH, and sodium chloride equivalency. This is done by using the appropriate equipment for each test as noted in Sections A to D above. To prepare a unit dose, the ingredients of such formulations generally will be dissolved in a solvent such as water or saline solution, in a volume between about 0.5 and 6.0 mls, more preferably between about 2 and 4 mls and most preferably between about 2.5 and 3.5 mls.

F. Surfactants:

The surface tension of a fluid is the tendency of the fluid to "stick" to itself when there is a surface between the liquid and the vapor phase (known as an interface). A good example is a drop of water falling in air. The drop assumes a spherical shape due to surface tension forces, which minimize its surface given the volume. Molecules at the surface of a liquid exert strong attractive forces on other molecules within their vicinity. The resultant force acting perpendicular to a line of unit length in the surface is known as surface tension, usually measured in Dynes/Centimeter.

Surfactants can be used as dispersing agents, solubilizing agents, and spreading agents. Some examples of surfactants are: PEG 400, Sodium lauryl sulfate, Spans (20-40-60 etc), Tweens (polysorbates, 20-40-60 etc), Tyloxapol, and Benzalkonium chloride. The purpose of using surfactants in the preferred formulations of the present invention is to adjust the surface tension of the aerosolized particles so that the maximum amount of medication is deposited in or near the middle meatus ostea. If the surface tension is

reduced too much, the majority of the particles will deposit in the nasal cavity, conversely if the surface tension is too high the particles go directly to the lungs without depositing in the nasal sinuses.

The HLB (hydrophille-lipophile-balance) is used to describe the characteristics of a surfactant. The system consists of an arbitrary scale to which HLB values are experimentally determined and assigned. If the HLB value is low, the number of hydrophilic groups on the surfactant is small, which means it is more lipophilic (oil soluble).

Surfactants can act as a solubilizing agent by forming micelles. For example, a surfactant with a high HLB would be used to increase the solubility of an oil in an aqueous medium. The lipophilic portion of the surfactant would entrap the oil in the lipophilic portion of the surfactant would entrap the oil in the lipophilic (interior) portion of the micelle. The hydrophilic portion of the surfactant surrounding of oil globule would, in turn, be exposed to the aqueous phase.

An HLB value of 10 or higher means that the agent is primarily hydrophilic, while an HLB value of less than 10 means it would be lipophilic. For example, spans have HLB values ranging from 1.8 to 8.6, which is indicative of oil soluble for oil dispersible molecules. Consequently, the oil phase will predominate and a water/oil emulsion will be formed. Tweens have HLB values that range from 9.6 to 16.7, which is characteristic of water-soluble or water dispersible molecules. Therefore, the water phase will predominate and oil/water emulsions will be formed.

Emulsifying agents are surfactants that reduce the interfacial tension between oil and water, thereby minimizing the surface energy through the formation of globules. Wetting agents, on the other hand, aid in attaining intimate contact between solid particles and liquids.

Detergents are also surfactants that reduce the surface tension and wet the surface as well as the dirt. When a detergent is used, the dirt will be emulsified, foaming may occur and the dirt will then wash away.

G. Pathogens Known to Produce Acute and Chronic Sinus Infections:

A retrospective review of sinus cultures obtained over a 4-year period from a consecutive series of patients who underwent endoscopic sinus surgery (ESS) was conducted by Niel Bhattacharyya M.D. *et al.*, *Archives of Otolaryngology –Head and Neck Surgery* Vol.125 No.10, October 1999. A wide range of bacteria may be present in the infected post-ESS sinus cavity, with a considerable population of gram-negative organisms, including *Pseudomonas* species. Fungal infections of the sinuses have a nonspecific clinical presentation, are refractory to standard medical treatment and may produce expansion and erosion of the sinus wall. Various factors have been implicated in the development of fungal sinusitis: anatomical factors in the osteomeatal complex, tissular hypoxia, traumatic factors, massive exposure to fungal spores, allergy and immunosuppression.

The most common bacterial organisms found are the following: Alpha Hemolytic *Streptococci*, Beta Hemolytic *Streptococci*, *Branhamella catarrhalis*, *Diphtheroids*, *Haemophilis influenzae* (beta-lactamase positive and negative), *Moraxella* species, *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, *Serratia marcescens*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

The most common fungal organisms found are the following: *Aspergillosis*, *Mucor* and *Candida Albicans*, *Fusarium*, *Curvularia*, *Cryptococcus*, *Coccidioides*, and *Histoplasma*.

The optimum treatment modality is for the physician to obtain a culture from the sinus cavities via endoscope or swab. The culture is sent to a laboratory where it is tested for minimum inhibitory concentration for several antibiotics and then the correct antibiotic can be chosen based on the sensitivities provided by the laboratory. Current therapy by most Otolaryngologists is to determine the best antibiotic by using their clinical experience in treating sinus infections. This is called empiric therapy.

The anti-fungal therapy is done similarly in that it can also be cultured and sent to the lab for identification allowing the most effective agent to be prescribed, or empiric therapy is performed by the physician.

The kill rate is determined by the susceptibility of the organism to the antibiotic or antifungals. If culture and sensitivities are performed, and the correct antibiotic is prescribed the kill rate occurs between a period of one to three weeks. The kill is determined/measured by a repeat culture and sensitivity test showing no bacterial or fungal growth (as appropriate).

II. Specific Embodiments

A. Pharmaceutical Compositions and Formulations

Preferred anti-infective agents include Penicillins, Cephalosporins, Macrolides, Sulfonamides, Quinolones, Aminoglycosides, BetaLactam antibiotics, Linezolid, Vancomycin, Amphotericin B, and Azole antifungals. Preferred anti-inflammatory agents include Glucocorticoids, Disodium Cromoglycate, and Nedcromil Sodium. Preferred anti-mucolytic agents are Acetylcysteine and Dornase Alpha. Preferred decongestant agents are Phenylephrine, Naphazoline, Oxymetazoline, Tetrahydrozoline, and Xylometoazoline. These agents may be found in the *American Hospital Formulary Service* published by American Society of Hospital Pharmacists, Inc., which is incorporated herein by reference.

As an example of a contemplated formulation, Cefuroxime is formulated in dosages of 285 mg in 3 ml sterile water for injection per dose, to produce an antibiotic for aerosol administration. This formulation may be compounded under a Laminar Flow hood by performing the following steps: 1) weigh out sufficient cefuroxime to provide 21 doses of 285 mg each (5985 mg), with 5% overage to account for that lost in compounding; 2) QS ad (add up to) to 63 ml with sterile water, with 5% overfill for loss in compounding; and 3) adding 0.1 ml of polysorbate 20 per 100 ml solution. The final compounded solution/mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

The formulation is tested using a Ring Tensiometer or the Capillary Rise test to determine the surface tension of the solution. The preferable range is 10 to 70 dynes/cm.

The formulation may be adjusted with a surfactant if necessary using, for example, polysorbate 20.

Using a pH meter, the formulation is tested for the desirable pH, preferably in the range of about 3.0 to 8.5. The pH is adjusted with appropriate acids, bases and appropriate buffers as needed according to conventional compounding practices.

Preferably the formulation will also be evaluated using E tables from sources known to practitioners skilled in the pharmaceutical arts, such as *Remington: The Science and Practice of Pharmacy* or other suitable pharmaceutical text to calculate its sodium chloride equivalence to ensure that it is in the preferred range of 0.9% to 3.0%. Similarly, the Osmolarity is checked to ensure that it falls within the preferred range of about 300 to 880 mOsm/kg. If Osmolarity falls outside of this range, the polysorbate 20 component may be decreased until the preferred conditions are met.

As a second example, Ciprofloxacin is formulated in dosages of 90 mg unit dose in 3 ml of sterile water for injection per dose. Because compounds of this antibiotic class (i.e., Fluoroquinolones) do not have inherent surfactant activities, a surfactant preferably is added to lower the surface tension of the final product.

This formulation may be compounded under a Laminar Flow hood by performing the following steps: 1) weighing out a sufficient quantity of Ciprofloxacin powder to prepare 28 doses (2520 mg) with 5% overage to account for loss during compounding; 2) QS ad to 74 ml sterile water for injection (add 5% overage for loss in compounding); and 3) adding 0.25 ml polysorbate 20 for every 100 ml of solution. The final compounded solution/mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and osmolarity within preferred ranges or to preferred levels.

As a third example, Amphotericin B is formulated in 10 mg unit doses along with Hydrocortisone sodium succinate in 50 mg unit doses in 3 ml sterile water to provide an antifungal agent together with an anti-inflammatory agent.

This formulation may be compounded under a Laminar Flow hood by performing the following steps: 1) weighing out sufficient powder of Amphotericin B to make 28 doses (280 mg) of 10 mg each allowing 5% overage for loss in compounding; 2) weighing out sufficient powder of Hydrocortisone sodium succinate to make 28 doses (1400 mg) of 50 mg each allowing 5% overage for loss of compounding; 3) combining powders; and 4) QS ad sterile water for injection to 84 ml plus 5% for loss in compounding. The final compounded solution/mixture is filtered using a 0.45 micron or 1 micron filter before placing in a unit of use (unit dose) container. A filter with a larger pore is necessary for filtering amphotericin.

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and osmolarity within preferred ranges or to preferred levels.

As a fourth example, Ofloxacin is formulated in 90 mg unit doses along with Acetylcysteine in 100 mg unit doses in 3 ml of sterile water to provide an antibiotic together with a mucolytic agent for injection.

This formulation is compounded under a Laminar Flow Hood by performing the following steps: 1) weighing out sufficient powder of Ofloxacin to make 28 doses (2520 mg) of 90 mg each allowing 5% overage for loss in compounding; 2) weighing out sufficient powder of Acetylcysteine to make 28 doses (2800 mg) of 100 mg each allowing 5% overage for loss in compounding; and 3) combining the powders and QS ad to 84 ml with sterile water for injection allowing 5% overage for loss during compounding. The final compounded solution/mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and osmolarity within preferred ranges or to preferred levels.

As a fifth example, Tobramycin is formulated in 100 mg unit doses in 2.5 ml of saline solution to provide an alternative antibiotic formulation. The formulation is compounded under a Laminar Flow hood by performing the following steps: 1) weighing

out sufficient tobramycin powder to provide 42 doses of 100 mg per dose (4200 mg), allowing for 5% overage due to losses during compounding; 2) QS ad with 105 ml of sterile water for injection, allowing for 5% overage due to losses during compounding; and 3) adding 0.15 ml polysorbate 20 to adjust surface tension. The final compounded solution/mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and osmolarity within preferred ranges or to preferred levels.

As a sixth example, Cefoperazone and Oxymetazoline are formulated in 3ml of Sterile water for injection to provide an antibiotic formulated with a decongestant. This formulation is prepared under a Laminar Flow Hood by following these steps: 1) weighing out sufficient powder of Cefoperazone to make 28 doses of 600mg each (16.8gm) allowing 5% overage for compounding loss; 2) weighing out sufficient powder of Oxymetazoline to make 28 doses of 0.5mg each (14mg) allowing 5% overage for compounding loss; 3) combining the powders together; 4) QS ad with sterile water to 84ml allowing 5% overage for compounding loss; 5) adding Benzalkonium Chloride 0.02% (0.02gm/100ml of solution). The final compounded solution/mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and osmolarity within preferred ranges or to preferred levels.

B. Determination of the Course of Treatment

In general, the course of treatment for any given patient will be determined by his or her physician. Thus, if the organisms found in a patient's sinuses are cultured by known techniques and their sensitivities are determined, the most appropriate antibiotic and/or will be ordered. However, if no cultures and sensitivities are done, then the patient also may be treated empirically with the antibiotic or antifungal chosen by the physician

using his or her experience based on what bacteria or fungus is suspected. If the anatomical structures inside the nasal passageways are swollen or inflamed due to allergy or flu symptoms, an anti-inflammatory agent and/or a decongestant agent also may be administered if the patient is not otherwise using nasal sprays or oral medication separately.

Example of a Patient Treatment Scenario:

1. Patient contracts what he/she feels is a sinus infection and goes to his/her Otolaryngologist for diagnosis. After determining the diagnosis of sinusitis, a culture is obtained endoscopically and sent to the laboratory.
2. The laboratory determines the bacteria/fungus sensitivities by drug and reports its findings to the physician.
3. The physician faxes the report to the pharmacy along with a prescription for the antibiotic most appropriate for the infection. The formulation is prepared as described above and dispensed in 2.5 ml containers. Generally, the container will be labeled: "Store in Refrigerator."
4. The physician will call patient and discuss the treatment and any pertinent data necessary to enhance the treatment outcome.

C. Contemplated and Preferred Treatment Regimens:

The preferred treatment is the antibiotic (adjusted for the proper surface tension, pH, sodium chloride equivalence, and osmolarity) that most effectively kills the bacteria or fungus as determined by culture and sensitivity, administered once to three times per day for a duration of 5 to 10 minutes per each treatment (See Table 1).

The total number of days needed to rid the infection preferably is determined by reculturing until no growth is noted. However, when the physician does not do culturing, the conventional standard of practice is two weeks of therapy until patient generally would be expected to have become asymptomatic plus an additional 7 days of therapy.

D. Monitoring Efficacy:

The typical Otolaryngologist when treating chronic sinusitis prescribes antibiotics until the patient is symptom free by physical exam plus an additional seven days. The problem that occurs with respect to sinus infections is that, if the infection is not completely resolved, the patient will have a recurrence the next time their immune system is challenged, *i.e.*, they contract the flu, go through a stressful time in their life or need chemotherapy treatments. Thus, the preferred method of determining resolution of the infection is to reculture the sinuses endoscopically and have the laboratory report come back negative, *i.e.*, reporting no growth of pathogenic microorganisms. The present inventors have discovered that aerosolization should lead to less resistance exhibited by bacteria due to the fewer times they are exposed to the antibiotic, and such exposure occurs at lower dosages and for shorter periods of time of aerosolized administration (typically 1-3 weeks) as compared to oral (typically 3 weeks to several months) and intravenous treatment (typically 3-6 weeks).

E. Equipment for Aerosolized Delivery of Pharmaceutical Composition:

Equipment for aerosolized delivery of pharmaceutical compositions are well known to the skilled artisan. O'Riordan *et al.*, *Journal of Aerosol Medicine*, 20(1): 13-23 (1997), reports the delivery of aerosolized tobramycin by a jet nebulizer and an ultrasonic nebulizer. U.S. Patent 5, 508, 269, issued April 16, 1996, compares the characteristics of three different nebulizers: the Ultraneb 99 (DeVilbiss) ultrasonic nebulizer, the Medicaid Sidestream jet nebulizer, and the Pari LC jet nebulizer.

The preferred equipment for aerosolized delivery of pharmaceutical solutions is depicted in Figure 1. This nebulizer manufactured by Pari Respiratory Equipment, Inc., for the inventors produces the desired particle size for effective administration of the solutions in this invention to the sinuses. To use this nebulizer, preferably 0.5 ml to 8 ml of medication solution, more preferably 2 ml to 4 ml and most preferably 2.5 ml to 3.5 ml of medication solution is placed in the nebulizer at A. The nebulizer is then connected

to a compressor or other source of 4 liter/minute airflow at B with tubing supplied. When the airflow is turned on the patient places the nose piece C under his/her nostrils and breathes normally until the medication solution in the nebulizer begins to sputter and no mist comes out at C. This will usually take 8 to 10 minutes.

In light of the foregoing general discussion, the specific examples presented below are illustrative only and are not intended to limit the scope of the invention. Other generic and specific configurations will be apparent to those persons skilled in the art.

EXAMPLES

Example 1: Patient A

A female in her forties had been suffering from sinusitis for most of her adult life. These sinusitis episodes seemed to be triggered by allergies. She historically had three-four (3-4) episodes of sinusitis each year, which were treated with oral antibiotics for four-eight (4-8) weeks per episode. These oral antibiotic regimens produced yeast infections, which were treated with Diflucan® (fluconazole). Relief from the headaches, malaise, facial pressure and pain, yellow-green nasal discharge, coughing and fever took up to six weeks and were treated with narcotic and non narcotic analgesics, decongestants, decongestant nasal sprays, cough suppressants, and nasal rinses. Her allergies were treated with antihistamines and anti-inflammatory agents.

In an effort to reduce the duration of her sinusitis episodes, a nose drop of tobramycin 80 mg/ml was administered. This treatment did not seem to work. The medication was irritating; and in order to administer the drops and try to get them into the sinus cavity, the patient had to hold her head back. This caused intolerable pain resulting in the discontinuation of the therapy. A nose drop of Bactoban® was tried. It was not efficacious; it was very viscous. The administration of this drop produced similar pain on administration, and this therapy was also discontinued.

In order to eliminate the pain caused by holding her head back when administering nose drops, a nose drop of tobramycin was administered after the patient had been on oral

antibiotics for a period of time. This did not seem to work. The drop did not seem to penetrate into the sinus cavities.

Thereafter, a preparation of tobramycin 80 mg/ml was administered using 3 ml in a Pari LC Star® nebulizer cup with adult mask attached and a Pari Proneb® compressor. The medication was nebulized three (3) times daily. After four days of therapy, the patient experienced a “dumping” of green, purulent nasal discharge. The therapy was continued for a total of seven (7) days. It seemed at this point that the sinus infection had been eliminated, but a relapse was experienced within a month. Another seven (7) day regimen of nebulized tobramycin was given to the patient. Again the sinus infection seemed to be eliminated, but it reoccurred within two (2) months.

A preparation of cefuroxime 285 mg in 2.5 ml sterile water for injection was administered three (3) times daily using a Pari LC Star® nebulizer cup with adult mask attached and a Pari Proneb® compressor. The time of nebulization was extensive and the medication did not seem to be completely nebulized. After one day of therapy, a Pari Turbo® compression was substituted for the Pari Proneb® compressor. The patient experienced a “dumping” of green, purulent nasal discharge after (3) days of therapy. The therapy was continued for a total of seven (7) days, again she contracted a yeast infection and was given Diflucan®.

After the seven (7) days of treatment with nebulized cefuroxime using the Pari Turbo® compressor and the Pari LC Star® nebulizer cup with mask, the patient has remained free of sinus infections for nine (9) months. She has continued to experience problems with her allergies, and while in the past these allergies triggered sinus infections, this time no such infection has recurred.

Example 2: Patient B

A male in his forties had been experiencing sinus infections off and on during his adult life. He was treated with cefuroxime 285 mg in 2.5 ml of sterile water for injection three (3) times daily using a Pari LC Star® nebulizer cup with adult mask attached and a Pari Turbo® compressor. The patient experienced a “dumping” of green, purulent nasal

discharge after eight (8) treatments. The therapy was continued for a total of seven (7) days. No other antibiotics were given. This patient has been free from sinus infections for six (6) months.

Example 3: Patient C

A female aged mid-fifty had been suffering from sinusitis off and on for most of her adult life. These sinusitis episodes seemed to be triggered by allergies. The patient took antihistamines and decongestants when allergies triggered headaches and/or a clear nasal discharge. Historically, she would have one or more sinus infections a year requiring twenty or more days of oral antibiotics.

She was treated with cefuoxime 285 mg in 2.5 ml of sterile water for injection three (3) times daily using a Pari LC Star® nebulizer cup with adult mask attached and a Pari Turbo® compressor. The patient experienced a “dumping” of green, purulent nasal discharge after eight (8) treatments. The therapy was continued form a total of seven (7) days. No other antibiotics were given. This patient has been free from sinus infections for six (6) months.

It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It therefore should be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All journal articles, other references, patents and patent applications that are identified in this patent application are incorporated by reference in their entirety.

Table 1
Agents and Dosages

Generic Name	Brand Name	Class	Preferable Range	More Preferable Range	Most Preferable Range	Most Preferable Dose
Amikacin	Amikin	Aminoglycoside	50-500mg	75-300mg	100-200mg	166mg Q8-12H
Amphotericin B	Fungizone	Antifungal	2.5-45mg	4-30mg	7.5-15mg	10mg Q12H
Azithromycin	Zithromax	Macrolide	50-400mg	75-300mg	150-200mg	167mg Q12H
Aztreonam	Azactam	Monobactam	250-1000mg	300-900mg	475-750mg	450mg Q8H
Cefazolin	Ancef, Kefzol	Cephalosporin (Gen I)	250-1000mg	300-900mg	575-700mg	650mg Q8H
Cefepime	Maxipime	Cephalosporin (Gen IV)	125-1000mg	200-900mg	575-700mg	650mg Q12H
Cefonicid	Moniacid	Cephalosporin (Gen II)	250-1000mg	300-900mg	575-700mg	600mg Q24H
Cefoperazone	Cefobid	Cephalosporin (Gen III)	250-1000mg	300-900mg	575-700mg	600mg Q12H
Cefotaxime	Claforan	Cephalosporin (Gen III)	250-1000mg	300-900mg	575-700mg	600mg Q8-12H
Cefotetan	Cefotan	Cephalosporin (Cepharmycin)	250-1000mg	300-900mg	575-700mg	600mg Q8-12H
Cefoxitin	Mefoxin	Cephalosporin (Cepharmycin)	250-1000mg	300-900mg	575-700mg	600mg Q12H
Ceftazidime	Fortaz, Ceptaz	Cephalosporin (Gen III)	250-1000mg	300-900mg	475-750mg	550mg Q12H
Ceftizoxime	Cefizox	Cephalosporin (Gen III)	250-1000mg	300-900mg	575-700mg	600mg Q8-12H
Ceftriaxone	Rocephin	Cephalosporin (Gen III)	250-1000mg	300-900mg	575-700mg	650mg Q12H
Cefuroxime	Ceftin	Cephalosporin (Gen II)	100-600mg	200-520mg	250-400mg	285mg Q8H
Cephapirin	Cefadyl	Cephalosporin (Gen I)	250-1000mg	300-900mg	575-700mg	650mg Q12H
Ciprofloxacin	Cipro	Quinolone	25-200mg	50-175mg	75-110mg	90mg Q12H
Clindamycin	Cleocin	Lincosamide	50-600mg	75-500mg	125-300mg	225mg Q12H
Doxycycline	Vibramycin	Tetracycline	10-100mg	15-80mg	25-65mg	27mg Q12H
Fluconazole	Diffucan	Antifungal	12.5-150mg	20-70mg	25-50mg	30mg Q12H
Gentamycin	Garamycin	Aminoglycoside	10-200mg	30-150mg	80-120mg	95mg Q8-12H
Itraconazole	Sporanox	Antifungal	12.5-150mg	20-70mg	25-50mg	30mg Q12H
Levofloxacin	Levaquin	Quinolone	40-200mg	50-150mg	60-80mg	70mg Q12H
Meropenem	Merrin	Carbapenem	200-750mg	250-700mg	300-500mg	333mg Q8H
Mezlocillin	Mezlin	Penicillin	300-1500mg	375-1000mg	750-950mg	833mg Q6H
Miconazole	Monistat	Antifungal	12.5-300mg	30-200mg	50-100mg	60mg Q12H
Nafcillin	Nafcil	Penicillin	100-1000mg	125-750mg	250-600mg	460mg Q6H
Ofloxacin	Floxin	Quinolone	25-200mg	50-175mg	75-110mg	90mg Q12H

Generic Name	Brand Name	Class	Preferable Range	More Preferable Range	Most Preferable Range	Most Preferable Dose
Piperacillin	Pipracil	Penicillin	100-1000mg	125-750mg	250-600mg	460mg Q6H
Rifampin	Rifadin	Miscellaneous	500-5000mg	1000-4000mg	1500-3500mg	2250mg Q12H
Ticarcillin + Clavulanate	Timentin	Penicillin	500-5000mg	1000-4000mg	1500-3500mg	2250mg Q6-8H
Tobramycin	Nebcin	Aminoglycoside	10-200mg	30-150mg	80-120mg	95mg Q8-12H
Vancomycin	Vancocin	Antifungal	50-400mg	75-325mg	125-250mg	166mg Q6-8H

CLAIMS

1. A pharmaceutical composition comprising one or more active ingredients selected from the group consisting of anti-infective, anti-inflammatory, and anti-mucolytic agents, wherein the surface tension of the solution is between about 10 to 70 dynes/cm, said composition being formulated as a solution in a unit dose for aerosol administration to the nasal sinuses and being packaged with directions for its use in the treatment of sinusitis.
2. The composition of claim 1, wherein the composition has a pH in the range of about 3.0 to 8.5.
3. The composition of claim 1, wherein the osmotic pressure of the solution between about 220 mOsm/kg to 880 mOsm/kg.
4. The composition of any of claims 1 to 3, wherein the NaCl equivalency to the solution is preferably between about 0.2% NaCl to 3.0% NaCl.
5. The composition of any of claims 1 to 4, wherein the composition further comprises a surfactant in addition to the one or more active ingredients.
6. The composition of any of claims 1 to 4, further comprising a decongestant.
7. The pharmaceutical composition of any one of claims 1-4, which when administered as an aerosolized spray has minimal systemic side effects.
8. The pharmaceutical composition of any one of claims 1-4, wherein said active ingredient is an anti-infective agent and the sinusitis is caused by a pathogen selected from the group consisting of Alpha Hemolytic *Streptococci*, Beta Hemolytic *Streptococci*,

Branhamella Catarrhalis, *Diphtheroids*, *Haemophilis influenzae* (beta-lactamase positive and negative), *Moraxella* species, *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Aspergillosis*, *Mucor* and *Candida Albicans*, *Fusarium*, *Curvularia*, *Cryptococcus*, *Coccidioides*, and histoplasma..

9. The pharmaceutical composition of claim 8, wherein said anti-infective agent is selected from the group consisting of Penicillins, Cephalosporins, Macrolides, Sulfonamides, Quinolones, Aminoglycosides, BetaLactam antibiotics, Linezolid, Vancomycin, Amphotericin B, and Azole antifungals.

10. The pharmaceutical composition of claim 5, wherein said surfactant is a polysorbate.

11. A kit containing a pharmaceutical composition of any one of claims 1-4, and a nebulizer cup with a nasal adapter for delivering the composition in aerosolized form to the nasal sinuses.

12. An aerosol comprising the pharmaceutical composition any of claims 1-4, wherein at least about 85% of the aerosolized particles have a Mass Median Aerodynamic Diameter within the range of about 0.5 to 10 microns.

13. An aerosol according to claim 12, wherein said aerosol is effective to kill at least about 90 % of susceptible sinusitis-causing pathogens present in the sinus passages of a sinusitis patient within about 14 days following an every 8 hr (TID), every 12 hr (BID), or every 24 hr (AD) administration protocol.

14. The combination of a nebulizer device and the kit of claim 11.

15. A method of treating a patient suspected or diagnosed as having chronic sinusitis comprising the step of administering to the patient the pharmaceutical composition of any of claims 1 to 4, by aerosolization using a nebulizer which delivers aerosol particles of between about 1 to 5 μm in average diameter.

16. The method of claim 15, wherein the nebulizer is a PARI nebulizer with a nasal adapter.

17. The method of claim 15, wherein the nebulizer is connected to a PARI SinuNEB compressor.

18. The method of claim 15, wherein the nebulizer delivers a majority of aerosolized particles in the size range of about 3.0 to 3.5 μm in diameter.

19. The method claim 15, wherein the pharmaceutical composition is administered to the patient 1-3 times a day for a total of 14-21 days.

20. The pharmaceutical composition of claim 10, wherein the polysorbate is selected from the group consisting of polysorbate 20 to polysorbate 85.

AMENDED CLAIMS

[received by the International Bureau on 15 November 2000 (15.11.00);
original claims 5-8, 11, 12 and 15 amended; other claims unchanged (3 pages)]

1. A pharmaceutical composition comprising one or more active ingredients selected from the group consisting of anti-infective, anti-inflammatory and anti-mucolytic agents, wherein the surface tension of the solution is between about 10 to 70 dynes/cm, said composition being formulated as a solution in a unit dose for aerosol administration to the nasal sinuses and being packaged with directions for its use in the treatment of sinusitis.
2. The composition of claim 1, wherein the composition has a pH in the range of about 3.0 to 8.5.
3. The composition of claim 1, wherein the osmotic pressure of the solution between about 300 mOsm/kg to 880 mOsm/kg.
4. The composition of any one of claims 1 to 3, wherein the NaCl equivalency to the solution is preferably between about 0.9% NaCl to 3.0% NaCl.
5. The composition of any one of claims 1 to 3, wherein the composition further comprises a surfactant in addition to the one or more active ingredients.
6. The composition of any one of claims 1 to 3, further comprising a decongestant.
7. The pharmaceutical composition of any one of claims 1-3, which when administered as an aerosolized spray has minimal systemic side effects.
8. The pharmaceutical composition of any one of claims 1-3, wherein said active ingredient is an anti-infective agent and the sinusitis is caused by a pathogen selected from the group consisting of Alpha Hemolytic *streptococci*, Beta Hemolytic *streptococci*,

Branhamella Catarrhalis, *Diphtheroids*, *Haemophilis influenzae* (beta-lactamase positive and negative), *Moraxella* species, *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Aspergillosis*, *Mucor* and *Candida Albicans*, *Fusarium*, *Curvularia*, *cryptococcus*, *coccidioides*, and histoplasma..

9. The pharmaceutical composition of claim 8, wherein said anti-infective agent is selected from the group consisting of Penicillins, Cephalosporins, Macrolides, Sulfonamides, Quinolones, Aminoglycosides, BetaLactam antibiotics, Linezolid, Vancomycin, Amphotericin B, and Azole antifungals.

10. The pharmaceutical composition of claim 5, wherein said surfactant is a polysorbate.

11. A kit containing a pharmaceutical composition of any one of claims 1-3, and a nebulizer cup with a nasal adapter for delivering the composition in aerosolized form to the nasal sinuses.

12. An aerosol comprising the pharmaceutical composition any one of claims 1-3, wherein at least about 85% of the aerosolized particles have a Mass Median Aerodynamic Diameter within the range of about 1.0 to 4.0 microns.

13. An aerosol according to claim 12, wherein said aerosol is effective to kill at least about 90 % of susceptible sinusitis-causing pathogens present in the sinus passages of a sinusitis patient within about 14 days following an every 8 hr (TID), every 12 hr (BID), or every 24 hr (AD) administration protocol.

14. The combination of a nebulizer device and the kit of claim 11.

15. A method of treating a patient suspected or diagnosed as having chronic sinusitis comprising the step of administering to the patient the pharmaceutical composition of any one of claims 1 to 3, by aerosolization using a nebulizer which delivers aerosol particles of between about 1 to 5 μ m in average diameter.

16. The method of claim 15, wherein the nebulizer is a PARI nebulizer with a nasal adapter.

17. The method of claim 15, wherein the nebulizer is connected to a PARI SinuNEB compressor.

18. The method of claim 15, wherein the nebulizer delivers a majority of aerosolized particles in the size range of about 3.0 to 3.5 μ m in diameter.

19. The method claim 15, wherein the pharmaceutical composition is administered to the patient 1-3 times a day for a total of 14-21 days.

20. The pharmaceutical composition of claim 10, wherein the polysorbate is selected from the group consisting of polysorbate 20 to polysorbate 85.

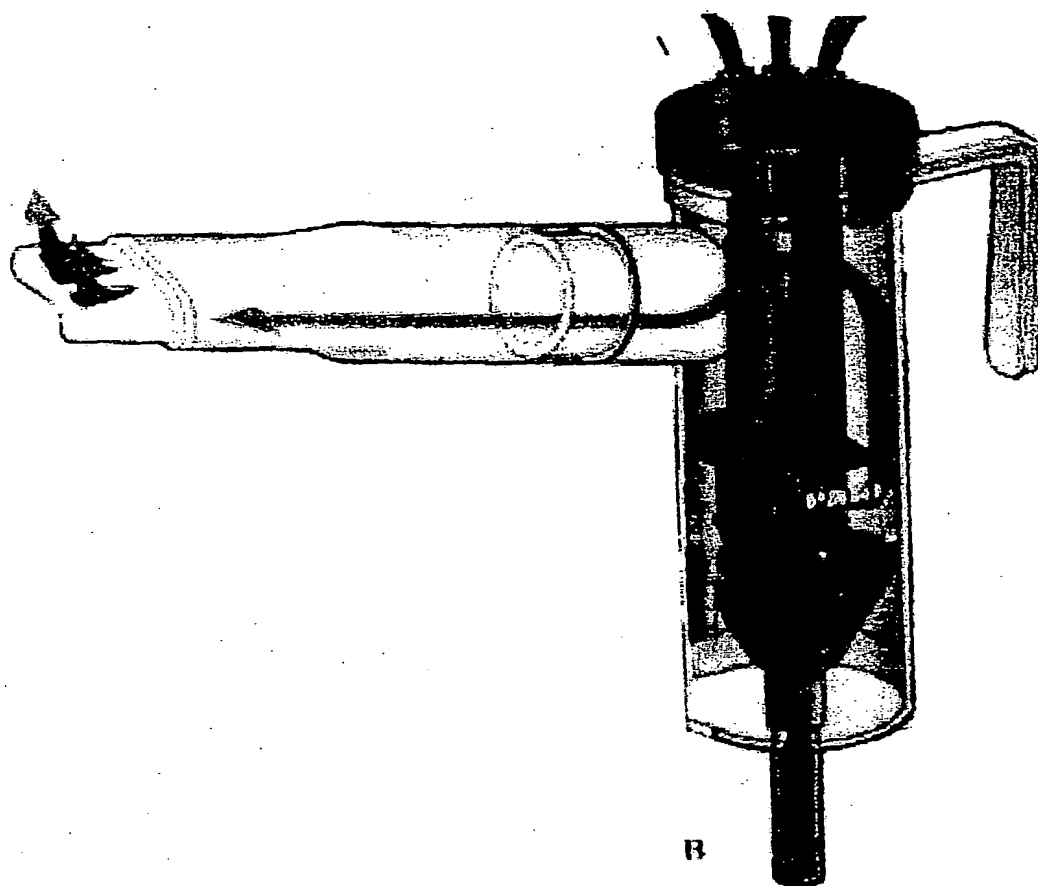


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18410

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61L 9/04

US CL : 424/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/45

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST 2.0, search terms: antibiotic or antiinfective, anti-inflammatory, anti-mucolytic or mucolytic, sinus?, inhalation or nebulizer, hypotonic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y ---- A	US 5,789,391 A (JACOBUS et al.) 04 AUGUST 1998 (04/08/98) see abstract, column 5, lines 37-55, column 6, lines 11-24, column 6, lines 44-51, see claim 4	1 ---- 2-4
Y, P ---- A, P	US 5,958,897 A (JACOBUS et al.) 28 SEPTEMBER 1999 (28/09/99) see abstract, column 6, lines 16-27, column 6, lines 38-42, column 6, lines 51-65, column 7, lines 13-26.	1 ---- 2-4
Y, P ---- A, P	US 5,972,904 A (JACOBUS et al.) 26 OCTOBER 1999 (26/10/99) see abstract, column 6, lines 41-52, column 7, lines 8-22, column 7, lines 43-50, see claim 4.	1 ---- 2-4

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 AUGUST 2000

Date of mailing of the international search report

20 SEP 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

DONNA JAGOE

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18410

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P ---- A, P	US 5,981,506 A (JACOBUS et al.) 09 NOVEMBER 1999 (09/11/99) see abstract, column 6, lines 34-45, column 7, lines 1-15, column 7, lines 36-42, see claim 4.	1 ---- 2-4
Y, P ---- A, P	US 5,925,334 A (RUBIN et al.) 20 JULY 1999 (20/07/99), see column 10, lines 5-59	1 ---- 2-4
Y	US 5,883,084 A (PETERSON et al.) 16 MARCH 1999 (16/03/99), column 6, lines 2-20, column 6, lines 49-60, column 7, line 36 to column 8, line 43.	1 ---- 2-4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/18410

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.